

# Multiscale Modeling of Multiple Myeloma Using Biocellion Framework

Chris Kang<sup>1</sup>, Simon Kahan<sup>1,2</sup>, Alexander Ratushny<sup>3</sup>  
<sup>1</sup>University of Washington, <sup>2</sup>Biocellion SPC, <sup>3</sup>Celgene Corporation

## Abstract

Our overall goal is to create multiscale models using the Biocellion platform that predict outcomes at cellular resolution for multiple myeloma when treated using pharmaceutical products whose mechanisms of action (MOA) have been well studied and for which quantitative relationships, preclinical and clinical data are publicly available. Here, we present our early approach and preliminary results on a 3d model of the bone marrow microenvironment that is based on previously published mathematical models and suitable for systematic characterization of optimal intervention strategies (i.e. combination therapies). Through refinement and integration of additional microenvironment component models, we expect the extensible Biocellion model we develop to become both more broadly applicable and increasingly predictive.

## Introduction

Multiple myeloma (MM) is a cancer of plasma B cells, which is most commonly symptomized by lytic bone disease [1]. The bone destruction is characterized by excessive expression of receptor activator for nuclear factor  $\kappa$  B ligand, (RANKL), which increases bone resorption in the vicinity of MM, resulting in the imbalance of osteoblasts (OBs) and osteoclasts (OCs) [2]. First, our goal is to understand the dynamics of OB-OC balance with its known cytokines and their signaling pathways, and recapitulate these models at multiscale level in the 3d modeled bone marrow. Second, we wish to explore possible T cell intervention strategies in the multi-faceted development and resistance of MM [3]. We model both the inner-workings and the treatments of MMs at the "large-scale" tissue-level in Biocellion to observe complex emergent behaviors in the system. In the early stage, we combine results and emulate previous known mathematical models in DKK1-Wnt-OPG/RANKL pathway [4][5][6][7] and the biophysical properties of myeloma initiating cell niches [8][9].

Biocellion is a high-performance C++ framework for agent-based modeling of biological systems. Biocellion allows users to model individual differentiated cells as discrete agents, their physio-mechanical interactions with one another, and the diffusion of cytokines (as partial differential equations) in 3d in computationally efficient manners (Figure 1). Biocellion allows modeling of MM microenvironment to be efficient and scalable.

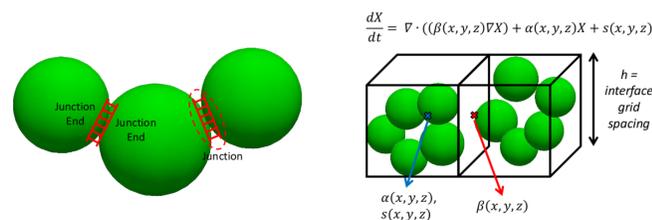


Figure 1. Example Biocellion features: a) Agent physio-mechanical interaction between agents b) Grid-level reaction-diffusion of molecules

## Model Specifics

Early stage model has eight agent types: OC, OB, MM, T cell (CD8+), bone marrow stromal cell (BMSC), myeloma initiating cell (MIC), T regulatory cell (Treg). The DKK1-Wnt-OPG/RANKL signaling pathway and the cell cycle parameters (apoptosis and proliferation) of OC-OB-MM follow the model used in [4]. Additionally, we employ the positive feedback loop that BMSCs and MICs create in the bone marrow niches [8][9]. The interaction causes higher expression of stromal cell-derived factor (SDF-1) in both BMSC and MICs, which promotes MM growth. Transforming growth factor beta (TGF $\beta$ ) is secreted by BMSCs which induces Treg. Treg inhibits MMs. Refer to (Figure 2).

When activated, CD8+ T cells form a TCR-antigen pathway with MM cells. The current model has PD-1 and PD-L1 checkpoints between T cells and MM. When the checkpoints form a pathway, the T cells do not engage with MMs (Figure 3a). When T cells are activated (i.e. immune checkpoint inhibitors are induced), cytotoxic T cells engage and promote apoptosis in the MMs (Figure 3b). Additionally, T cells secrete interferon gamma (IFN $\gamma$ ) which is known to target OCs, but indirectly stimulates OC formation.

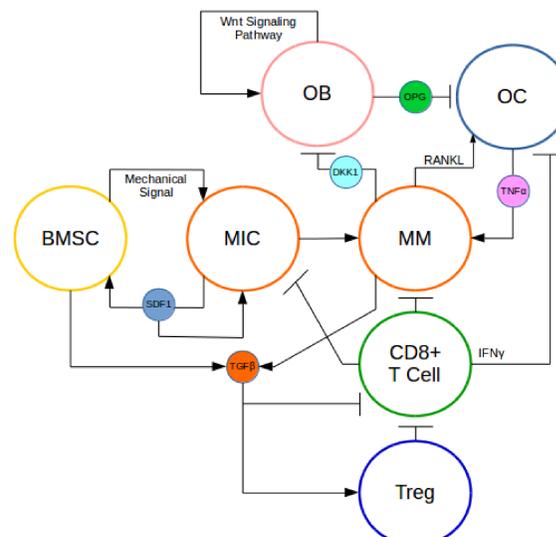


Figure 2. Model Signaling Pathways

## Biocellion

In Biocellion, each agent type is modeled as a sphere of varying radius with voxel coordinates. Additionally, each agent has user-defined state properties (i.e. cell cycle state). The model is created on a 128 x 128 x 128 simulation periodic-boundary-conditioned domain with 20  $\mu$ m grid box unit size. Biocellion allows fast and efficient modeling of the cytokine secretions with its built-in Partial Differential Equation reaction-diffusion solver. It supports adaptive mesh refinement (AMR) to increase/decrease refinement level. One can also compute physio-mechanical interactions between nearby agents in Biocellion, such as the checkpoint inhibition between MMs and T cells, and adhesion of BMSCs and MICs.

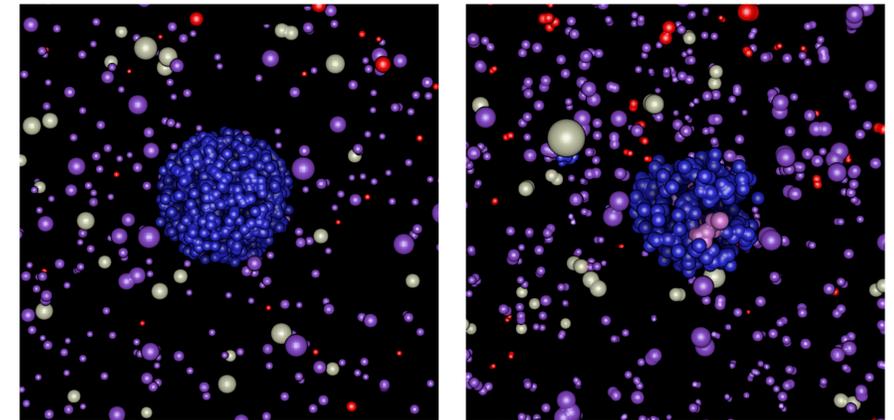


Figure 3. a) Unblocked PD-1/PD-L1 pathway resulting in MM growth b) Checkpoint Blocked (activated) T cells initiating MM apoptosis

## Discussion

In the current model, the apoptosis and proliferation of each cell type is highly dependent on initial conditions. A highly likely cause is the lack of incorporations of all cytokine receptors of each agent party and a high number of model parameters. With full mapping of the cytokine pathways as well as differentiation of cell types in the future works, we feel that the model sensitivity can be improved over time. For example, it is shown that osteoblasts and osteoclasts can be differentiated by stages of development. Immature OBs can support the growth of MMs, while, mature OBs enhance apoptosis of MMs [5]. The dynamical systems of differentiated OB-OC concentrations as explored by [6] would result in more reproducible results of bone marrow microenvironment. Additionally the functionalities of different types of activated T cells (CD4+ and CD8+) partake different roles in inhibiting MMs. In future works, we plan to utilize uncertainty and sensitivity analysis of the whole system to validate the bone marrow microenvironment [10]. Additionally, we plan to include key factors that impact RANKL and OPG such as interleukin-6 (IL-6), parathyroid hormone (PTH), and small leucine-rich proteoglycans (SLRPs) in our model, as discussed in [5][6][7].

## Conclusions

While the research is in its early stage, our aim is to successfully model the known signaling pathways and their dynamics in the bone marrow microenvironment. We hope to verify the simulation with experimental data at a 3d level with bone marrow structure. In doing so, we hope to discover possible immune checkpoint combination therapies and other targeted intervention strategies that do not result in relapse of MMs. Success with Biocellion would provide an *in silico* alternative faster and cheaper than the *in vitro* pre-clinical experiments that are currently performed to increase success rates of costly pharmaceutical trials.

## Contact

Chris Kang  
 Applied Mathematics,  
 University of Washington  
 Email: shinwook@uw.edu

**W** APPLIED MATHEMATICS  
 UNIVERSITY of WASHINGTON

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